PATENT SPECIFICATION

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A5B 332 33Y 38Y 390 420 422 424 426 42Y 431 433 43Y 481 482 483 48Y 492 493 49Y 511 51Y 523 52Y 540 542 543 54Y 565 566 56Y 586 58Y 650 651 65Y

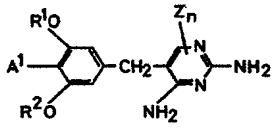
(19)

(54) BENZYLPYRIMIDINE DERIVATIVES

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company, of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to benzylpyrimidine derivatives. More particularly, the invention is concerned with 2,4 - diamino - 5 - benzylpyrimidine derivatives, a process for the manufacture thereof and antibacterial compositions containing same.

The benzylpyrimidine derivatives provided by the present invention are compounds of the general formula



(I)

wherein R^1 and R^2 each represent an alkyl or alkenyl group, Z represents an oxygen atom bonded to one of the cyclic nitrogen atoms, n stands for zero or 1 and A^1 represents a trifluoromethyl group or a group of the formula

(a) (b)

in which R^6 represents an oxygen atom and R^7 represents a hydrogen atom or an alkyl or alkoxy group; or 6^6 represents a hydroxyimino group and R^7 represents an alkyl group; or R^8 together with R^7 and the carbon atom to which they are attached represent a nitrilo group; R^8 and R^9 each represent a hydrogen atom or an alkyl group and R^{10} represents a hydroxy, alkoxy or $-N(R^3)(R^4)$ group; or R^9 and R^{10} each represent an alkoxy or alkylthio group, or R^9 together with R^{10} represent an alkylenedioxy or alkylenedithio group; and R^3 and R^4 each represent a hydrogen atom or an alkyl or alkanoyl group,

and acid addition salts thereof.

The term "alkyl" as used in this description and in the acompanying claims denotes a straight-chain or branched-chain saturated aliphatic hydrocarbon group containing at most 4 carbon atoms (e.g. methyl, ethyl and propyl). The term "alkenyl" means a straight-chain or branched-chain olefinically unsaturated hydrocarbon group containing up to 3 carbon atoms (e.g. allyl). The term "alkanoyl" means an alkanoyl group derived from a straight-chain or branched-chain alkanecarboxylic acid containing up to 4 carbon atoms (e.g. formyl and acetyl). The term "alkylenedioxy" or "alkylenedithio" means such groups containing 2 or 3 carbon atoms.

The group of formula (a) hereinbefore includes, in particular, the following groups: cyano, alkoxycarbonyl, N-hydroxyiminoalkyl, formyl and alkylcarbonyl.

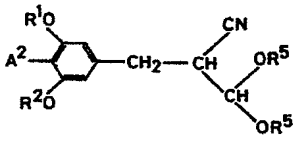
The group of formula (b) hereinbefore includes, in particular, the following groups: alkyl - dialkoxymethyl, alkyl - alkylenedioxymethyl, alkyl - dialkylthiomethyl, alkyl - alkylenedithiomethyl, hydroxymethyl which may be

C-monoalkylated or dialkylated, alkoxymethyl which may be C-monoalkylated or dialkylated, aminomethyl which may be C-monoalkylated or dialkylated, alkylaminomethyl which may be C-monoalkylated or dialkylated and dialkylaminomethyl which may be C-monoalkylated or dialkylated.

An especially preferred class of compounds of formula I hereinbefore comprises those in which R^1 and R^2 each represent an alkyl group, especially a methyl or ethyl group. Also preferred are those compounds of formula I in which A^1 represents a hydroxymethyl group which is C-monoalkylated or dialkylated, an alkoxymethyl group which may be C-monoalkylated or dialkylated or an alkylcarbonyl group.

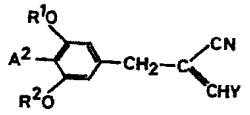
According to the process provided by the present invention, the benzylpyrimidine derivatives aforesaid (i.e. the compounds of formula I and their acid addition salts) are manufactured by

a) reacting a compound of the general formula



(IIa)

or



(IIb)

wherein R^5 represents an alkyl group, Y represents a leaving group and A^2 represents a trifluoromethyl group or a group of the formula

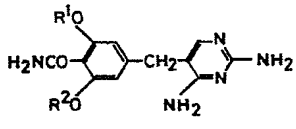
(c) (d)

in which R^{11} represents an oxygen atom and R^{12} represents an alkoxy group; or R^{11} together with R^{12} and the carbon atom to which they are attached represent a nitrilo group; R^{13} represents a hydroxy, alkoxy or $-N(R^3)(R^4)$ group; and R^1, R^2, R^3, R^4, R^8 and R^9 have the significance given earlier,

with guanidine,

or

b) dehydrating a compound of the general formula



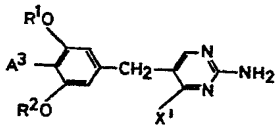
(III)

wherein R^1 and R^2 have the significance given earlier,

to the corresponding nitrile,

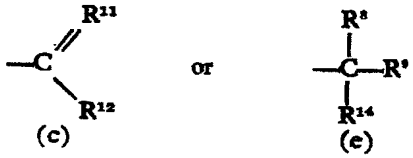
or

c) reacting a compound of the general formula



(IV)

wherein X′ represents a chlorine or bromine atom or an alkylthio or alkylsulphonyl group and A^3 represents a trifluoromethyl group or a group of the formula



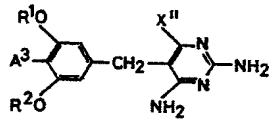
(c) (e)

in which R^{11} represents an oxygen atom and R^{12} represents an alkoxy group; or R^{11} together with R^{12} and the carbon atom to which they are attached represent a nitrilo group; and R^{14} represents an alkoxy or $-N(R^3)(R^4)$ group; or R^9 together with R^{14} represent an alkylenedioxy group, and R^1, R^2, R^3, R^4, R^8 and R^9 have the significance given earlier,

with ammonia,

or

d) replacing the substituent denoted by X″ in a compound of the general formula



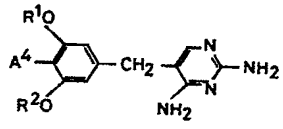
(V)

wherein R^1, R^2 and A^3 have the significance given earlier and X″ represents a chlorine or bromine atom or a hydroxy group,

by a hydrogen atom,

or

e) reductively cleaving the group A^4 in a compound of the general formula

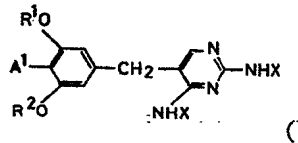


(VI)

wherein A^4 represents the group —CO—CH(R^8)—SO_2—CH_3, —COCH(R^8)— SO_2— phenyl or —CO—CH(R^8)—SO—CH_3 and R^1, R^2 and R^8 have the significance given earlier, to the acetyl group,
or

f) subjecting a compound of formula I hereinbefore in which n stands for zero to N-oxidation,
or

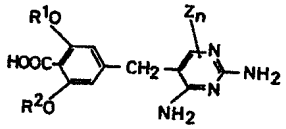
g) cleaving off the amino-protecting group or groups in a compound of the general formula



(VII)

wherein X represents a hydrogen atom or an amino-protecting group (at least one X representing an amino-protecting group), and R^1, R^2 and A^1 have the significance given earlier,
by hydrolysis or hydrogenolysis,
or

h) subjecting the carboxyl group in a compound of the general formula



(Ia)

wherein R^1, R^2, Z and n have the significance given earlier,
to esterification or to reduction to the aldehyde group,
or

i) subjecting the carbonyl group in a compound of formula I in which A^1 represents an alkylcarbonyl group and R^1, R^2, Z and n have the significance given earlier to condensation with hydroxylamine to give the hydroxyimino group, or to reductive amination, or to reduction to give the alcohol, or to ketalisation or thioketalisation, or to reaction with a Grignard compound to give a homologous alcohol,
or

j) subjecting the alkoxycarbonyl group in a compound of formula I hereinbefore in which A^1 represents an alkoxycarbonyl group and R^1, R^2, Z and n have the significance given earlier to reaction with a Grignard compound to give the ketone or the secondary or tertiary alcohol or to reduction to give the alcohol,
or

k) alkylating an alcohol function contained in A^1 in a compound of formula I hereinbefore or oxidising said function to give the carbonyl group,
or

l) reducing a nitrile group denoted by A^1 in a compound of formula I hereinbefore to give the aminomethyl group or to give the aldehyde group,
or

m) cleaving off a ketal or thioketal group contained in A^1 in a compound of formula I hereinbefore,
or

n) hydrolysing off the acyl group present in a compound of formula I in which A^1 represents a group of the formula

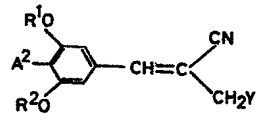
$$—CH_2—N(R^8)—COR^5$$

wherein R^5 and R^8 have the significance given earlier,
and, if desired, converting a base obtained into an acid addition salt.

According to embodiment (a) of the process provided by the present invention, a compound of formula IIa or IIb is reacted with guanidine. The symbol Y in a compound of formula IIb represents a leaving group. Examples of suitable leaving groups are ether groups (e.g. alkoxy groups such as methoxy, ethoxy, propoxy etc), thioether groups (e.g. alkylthio groups) or aliphatic, aromatic or heterocyclic amino groups such as alkylamino, benzylamino, arylamino (e.g. anilino which may be substituted or naphthylamino), dialkylamino, pyrrolidino, piperidino, piperazino and morpholino. The preferred leaving group is an anilino group which may carry in the phenyl ring one or more halogen, alkyl or alkoxy substituents.

The reaction of a compound of formula IIa or IIb with guanidine can be carried out according to methods known per se; for example, as described in Belgian Patent Specifications Nos. 594,131, 671,982 and 746,846. For example, the reaction can be carried out in a solvent such as an alkanol (e.g. methanol or ethanol), dimethylformamide, dimethyl sulphoxide or N - methyl - pyrazolone at a temperature in the approximate range of from 25°C to 200°C, preferably at a temperature of from 50°C to 170°C.

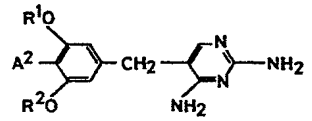
The compounds of formula IIb can be formed in situ under the conditions of the reaction from the tautomeric compounds of the general formula



(IIc)

wherein R^1, R^2, A^2 and Y have the significance given earlier.

The compounds of formula I which can be obtained according to embodiment (a) of the present process have the following general formula

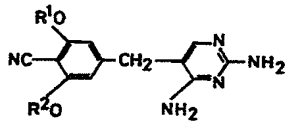


(Ib)

wherein R^1, R^2 and A^2 have the significance given earlier.

The dehydration of an acid amide of formula III in accordance with embodiment (b) of the present process can be carried out by treatment with a dehydrating agent such as phosphorus oxychloride, thionyl chloride, phosphorus pentoxide or polyphosphoric acid. The dehydration can be carried out in an inert organic solvent (e.g. pyridine), but the dehydrating agent can itself serve as the solvent.

Embodiment (b) of the present process leads to compounds of the general formula

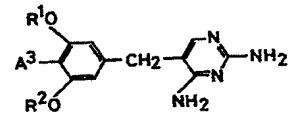


(Ic)

wherein R^1 and R^2 have the significance given earlier.

In acocrdance with embodiment (c) of the present process, a compound of formula IV is reacted with ammonia, the substituents denoted by X′ present in the pyrimidine ring being replaced by an amino group. The reaction is conveniently carried out in an alkanolic solution, especially a methanolic solution. In a preferred aspect, the reaction is carried out using methanolic ammonia. The reaction is conveniently carried out at a temperature between about 80°C and 200°C, especially at a temperature between about 100°C and 150°C. Since these temperatures lie above the boiling point of methanol, the reaction is then carried out in a closed system (e.g. in an autoclave).

In accordance with embodiment (c) of the present process, there are obtained compounds of the general formula



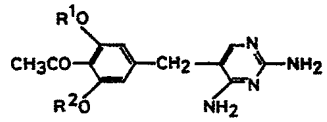
(Id)

wherein A^3, R^1 and R^2 have the significance given earlier.

The replacement of the bromine or chlorine atom present in a compound of formula V by a hydrogen atom in accordance with embodiment (d) of the process can be carried out by treatment with a reducing agent such as hydrogen iodide or catalytically activated hydrogen (e.g. palladium in alcohol) or with zinc and glacial acetic acid. Where X″ in a compound of formula V represents a hydroxy group, the compound is first reacted with cyanogen bromide in the presence of triethylamine and the reaction product is hydrogenated in the presence of palladium-on-carbon. There are thereby obtained compounds of formula Id hereinbefore.

The cleavage of the sulphonyl or sulphoxide group present in a compound of formula VI in accordance with embodiment (e) of the process can be carried out by treatment with aluminium amalgam in tetrahydrofuran/water, if desired while warming, or by means of zinc/acetic acid.

Embodiment (e) of the present process leads to compounds of the general formula



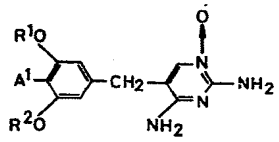
(Ie)

wherein R^1 and R^2 have the significance given earlier.

The N-oxidation of a compound of formula I hereinbefore in which n stands for zero in accordance with embodiment (f) of the present process can be carried out according to methods known per se using a customary N-oxidation agent. Especially preferred N-oxidation agents are perbenzoic acids, particularly m-chloroperbenzoic acid. The N-oxidation can be carried out, for example, in an inert solvent such as a chlorinated hydrocarbon (e.g. chloroform or methylene chloride), an alkanol (e.g. methanol or ethanol), dimethylformamide, dimethyl sulphoxide, water or dioxane. The oxidation is conveniently carried out at a temperature between room temperature and the boiling point of the solvent, expediently at a temperature between about 10°C and about 60°C. A temperature of about 10°C to about 20°C is preferred.

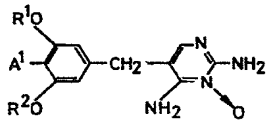
A N-oxide obtained can be isolated from the oxidation mixture in the usual manner. When m-chloroperbenzoic acid or perbenzoic acid is used as the N-oxidation agent, it has been found to be convenient to extract the oxidation mixture with a weak aqueous-alkaline solution (e.g. aqueous sodium bicarbonate solution), to acidify the aqueous extract obtained in order to precipitate the excess acid and, after removal of the excess acid by filtration, to make the filtrate neutral or slightly basic.

The N-oxidation leads, as a rule, to mixtures of N_1- and N_3-oxides of the general formulae



(If-1)

or



(If-2)

wherein R^1, R^2 and A^1 have the significance given earlier.

The separation and purification of the foregoing isomeric products can be carried out by chromatography (e.g. column chromatography) and/or recrystallisation, preferably from polar solvents such as alkanols, water etc.

In the compounds of formula VII which are used as starting materials for embodiment (g) of the present process, at least one of the X-symbols represents an amino-protecting group which can be converted into a free amino group by hydrolysis or hydrogenolysis. Examples of amino-protecting groups which can be converted into a free amino group by hydrolysis are acyl groups (e.g. alkanoyl groups such as formyl, acetyl, propionyl etc) and aroyl groups (e.g. benzoyl) or tertbutyloxycarbonyl. A group which can be converted into a free amino group by hydrogenolysis is, for example, the carbobenzoxy group. The preferred amino-protecting groups are acyl groups, especially the acetyl group.

The hydrogenolysis of an amino-protecting group denoted by X can be carried out, for example, catalytically, for example by means of palladium-on-carbon and in a solvent (e.g. an alkanol such as methanol) at a temperature of 10°—50°C, preferably at room temperature.

The hydrolysis of a compound of formula VII can be carried out by means of alkali (e.g. aqueous or aqueous-alcoholic alkali such as methanolic alkali) or by means of acid (e.g. aqueous or aqueous-alkanolic mineral acids such as hydrochloric acid).

The esterification of the carboxyl group present in a compound of formula Ig in accordance with embodiment (h) of the process can be carried out in a manner known per se by reacting a reactive acid derivative with an alkanol in the presence of a condensation agent such as an alkali metal alkoxide or a strong acid (e.g. hydrochloric acid). The reduction of the carboxyl group to give the aldehyde group, also in accordance with embodiment (h) of the present process, can be carried out, for example, with a complex metal hydride via the acid chloride.

The reduction of a carbonyl group in accordance with embodiment (i) of the present process can be carried out by means of a complex metal hydride such as sodium borohydride in an aqueous alkanol. The reductive amination can be carried out using an amine and Raney-nickel in an inert solvent (e.g. ethanol).

The reduction of an alkoxycarbonyl group to give the hydroxymethyl group in accordance with embodiment (j) of the process can be carried out using diisobutyl-aluminium hydride in dioxane.

The oxidation of an alcohol function in accordance with embodiment (k) of the present process can be carried out, for example, using an oxidation agent such as chromium trioxide in pyridine.

The reduction of a nitrile group in accordance with embodiment (l) of the process can be carried out using a complex metal hydride such as lithium aluminium hydride in ether (for the manufacture of compounds of formula I in which A^1 represents an aminomethyl group) or using diisobutyl-aluminium hydride in dioxane (for the manufacture of compounds of formula I in which A^1 represents a formyl group).

The cleavage of a ketal or thioketal group in accordance with embodiment (m) of the present process can be carried out using an aqueous acid, if desired while warming. The cleavage of a thioketal group is preferably carried out using Hg^{2+}.

Aqueous and aqueous-alcoholic mineral acids are preferably used for the hydrolysis in accordance with embodiment (n) of the process.

The starting materials used in embodiments (a) to (e) of the process, insofar as they are not known or insofar as they are not described hereinafter, can be prepared in a manner analogous to that described in the Examples hereinafter or according to the methods outlined in the following Table in which R^1, R^2, R^3, A^2, A^3, A^4 and Y have the significance given earlier. Compounds of formulae IIa, IIb, III and V are claimed *per se* in the specifications of our Divisional Applications Nos. 4559/76 (Serial No. 1455737), 4560/76 (Serial No. 1455738), 4561/76 (Serial No. 1455739), and 4562/76 (Serial No. 1455740), respectively.

TABLE

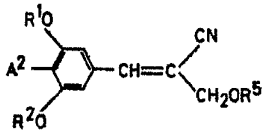
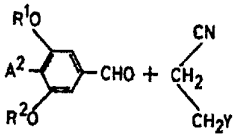
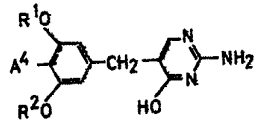
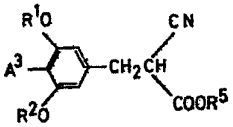
Starting material	Prepared from	Reaction	Literature
IIb		Alkanol and alkali metal alkoxide	Belgian Patent Specification No. 671,982
IIa	IIb	Alkanol addition	
IIb IIc		Condensation in strong alkaline medium	Belgian Patent Specifications Nos. 594,131 and 746,846

TABLE (Continued)

Starting material	Prepared from	Reaction	Literature
IV		Halogenation	Belgian Patent Specification No. 565,002
V		1) Condensation with guanidine in an alkaline medium 2) Replacement of the hydroxyl by bromine or chlorine using a phosphorus halide or oxyhalide	DOS 2003578

The compounds of formula I can be converted into acid addition salts, especially those which are customary in pharmaceutical preparations, by treatment with inorganic acids (e.g. hydrochloric acid, sulphuric acid, phosphoric acid etc) or organic acids (e.g. formic acid, acetic acid, succinic acid, lactic acid, citric acid, maleic acid, fumaric acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid).

The benzylpyrimidine derivatives provided by the present invention (i.e. the compounds of formula I hereinbefore and their acid addition salts) possess antibacterial activity. They inhibit the bacterial dihydrofolate reductase and potentiate the antibacterial activity of sulphonamides such as, for example, sulphisoxazole, sulphadimethoxine, sulphamethoxazole, 4 - sulphanilamido - 5,6 - dimethoxy - pyrimidine, 2 - sulphanilamido - 4,5 - dimethyl - pyrimidine, sulphaquinoxaline, sulphadiazine, sulphamonomethoxine and isosulphisoxazole and other inhibitors for enzymes which are involved in the folic acid biosynthesis such as, for example, pteridine derivatives. Thus, the present invention also provides an antibacterial composition which contains a benzylpyrimidine derivative of formula I hereinbefore, in association with a compatible carrier material and preferably also with an antibacterially active sulphonamide.

A combination of one or more of the benzylpyrimidine derivatives aforesaid with sulphonamides can be used in human medicine in a form adapted for oral, rectal or parenteral administration. The ratio of a compound of formula I to a sulphonamide can vary within a wide range; for example, between 1:40 (parts by weight) and 5:1 (parts by weight), the preferred ratio being between 1:1 and 1:5.

Thus, for example, a tablet can contain 80 mg of a compound of formula I and 400 mg of sulphamethoxazole, a tablet for children can contain 20 mg of a compound of formula I and 100 mg of sulphamethoxazole and a syrup (per 5 ml) can contain 40 mg of a compound of formula I and 200 mg of sulphamethoxazole.

The following Examples illustrate the process provided by the present invention:

Example 1.

8 g of sodium metal were dissolved, with the exclusion of moisture, in 200 ml of absolute methanol in a 2 litre flask provided with a magnetic stirrer and reflux condenser.

24.7 g of guanidine hydrochloride were added to this solution and the resulting suspension was stirred at room temperature for 30 minutes. The sodium chloride was filtered off under a vacuum and washed with ca 10 ml of cold absolute methanol. The filtrate was treated with 46 g of 4 - (3 - anilino - 2 - cyano - allyl) - 2,6 - dimethoxy - benzoic acid methyl ester and 1000 ml of isopropanol and the resulting suspension was heated at reflux for 50 hours while stirring. The mixture was concentrated, cooled and the precipitated crystals were filtered off under suction.

After crystallisation from ca 4 litres of methanol with the addition of ca 1 g of carbon, there was obtained α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester of melting point 250°—251°C.

The starting material was prepared as follows:

A mixture of 271 g of 2,6 - dimethoxy - terephthalic acid 1-monomethyl ester, 1.2 litres of absolute benzene, 100 ml of thionyl chloride and 30 ml of dimethylformamide were boiled at reflux for 2 hours with the exclusion of moisture. The resulting solution was evaporated to dryness in vacuo, the residue dissolved twice in ca 100 ml of absolute benzene and the solvent again removed in vacuo. After recrystallisation from 7 litres of hot n-heptane, the residue gave 260 g of acid chloride of melting point 100°—101°C. After concentration of the mother liquors, a further 20 g of acid chloride of melting point 90—95°C was obtained.

40 g of the foregoing acid chloride were dissolved in 400 ml of xylene dried over sodium. While gassing with nitrogen, 4 g of 5% palladium/barium sulphate and 0.4 ml of quinoline-sulphur regulator were added, nitrogen was bubbled through the resulting suspension for a further 10 minutes and then hydrogen was led through at 110°C. The course of the reaction was followed by titration of the resulting hydrochloric acid. After ca 2 hours (90% of the theoretical amount of hydrochloric acid being liberated), the reaction was interrupted, the suspension cooled under nitrogen and the catalyst filtered off under suction. The filtrate was concentrated to dryness in vacuo, the residue taken up in 150 ml of benzene and shaken out with 500 ml of ca 37% sodium bisulphite solution for 2 hours. The benzene phase was separated and the aqueous phase washed with 100 ml of benzene.

The aqueous solution remaining was cooled to 5°C and then adjusted to ca pH 10 with ca 20% sodium hydroxide solution. The precipitated aldehyde (and inorganic salts) were filtered off under suction. The solid material was taken up in 400 ml of benzene and 700 ml of water, the benzene solution separated and the aqueous phase extracted twice with 100 ml of benzene each time. The combined benzene extracts were washed with two 50 ml portions of water, dried over magnesium sulphate and evaporated to dryness in vacuo, 2,6 - dimethoxy - 4 - formyl - benzoic acid methyl ester of melting point 113—114°C being obtained.

The solvent was evaporated under nitrogen

and with the exclusion of moisture from a solution of 0.9 g of sodium metal in 15 ml of absolute methanol. The resulting sodium methylate was suspended in a solution of 25.2 g of β - mortholino - propionitrile in 28 ml of dimethyl sulphoxide (dried over molecular sieves) and the mixture was warmed to 70°C. At this temperature, a solution of 30 g of 2,6 - dimethoxy - 4 - formyl - benzoic acid methyl ester in 45 ml of anhydrous dimethyl sulphoxide was added dropwise over a period of 30 minutes and the mixture was subsequently stirred for a further 30 minutes at 75°C. After this time, almost no aldehyde could be detected. The solution was cooled to +5°C and treated dropwise with ca 30—40 ml of water, seeded and stirred for a further ca 3 hours. The crystalline product was filtered off under suction, washed with ca 15 ml of methanol cooled to 0°C and recrystallised from methanol. The resulting 4 - (2 - cyano - 3 - morpholine - allyl) - 2,6 - dimethoxy - benzoic acid methyl ester had a melting point of 137°—138°C.

8.6 g of aniline were treated, while cooling, with 7.6 ml of concentrated hydrochloric acid. There were subsequently added 32 g of 4 - (2-cyano - 3 - morpholino - allyl) - 2,6 - dimethoxy - benzoic acid methyl ester and 100 ml of isopropanol. The resulting suspension was heated at reflux for 30 minutes while stirring. About one third to one half of the solvent was evaporated off, 20 ml of water were added, the crystalline product was filtered off under suction, washed with a small amount of cold methanol and dried. Recrystallisation from methanol yielded 4 - (3 - anilino - 2 - cyano - allyl) - 2,6 - dimethoxy - benzoic acid methyl ester of melting point 193°—194°C.

Example 2.

A solution of 30 mg of sodium metal in 3 ml of absolute methanol was treated with 0.12 g of guanidine hydrochloride and the resulting suspension was stirred for 15 minutes. Thereafter, 0.29 g of 4 - (3,3 - dimethoxy - 2 - cyano - propyl) - 2,6 - dimethoxy - benzoic acid methyl ester was added and the mixture was heated at reflux for 18 hours. The methanol was then evaporated in vacuo and the basic product dissolved in 1-N acetic acid. The solution was filtered, made alkaline with concentrated amomnia while cooling, the α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester filtered off under suction and recrystallised from methanol; melting point 247°—248°C.

The starting material was prepared as follows:

11.2 g of 2,6 - dimethoxy - 4 - formyl - benzoic acid methyl ester were added under nitrogen to a solution, cooled to 5°C, of 3.45 g of sodium metal in 47 ml of absolute methanol. With vigorous stirring, a solution of 6.6 ml (0.1 M) of acrylonitrile in 3 ml of methanol were then added dropwise over a period of ca 20 minutes in such a manner that the temperature did not rise above 20°C. The mixture was stirred at room temperature for 17 hours and then evaporated to dryness. The residue was taken up in 200 ml of water and 200 ml of ether. The aqueous phase was extracted several times with ether. The ether phase was dried and concentrated (10 g). Column chromatography (400 g of silicagel; eluant:ether) yielded 4 - (3,3 - dimethoxy - 2 - cyano - propyl) - 2,6 - dimethoxy - benzoic acid methyl ester of melting point 90°—92°C (from methanol).

Example 3.

5.4 g of guanidine carbonate were added under nitrogen to a solution of 0.7 g of sodium metal in 9 ml of absolute methanol. The suspension was stirred at 80°C for 30 minutes and, after cooling to room temperature, treated with a solution of 3.5 g of 4 - (2 - cyano - 3 - morpholino - allyl) - 2,6 - dimethoxy - benzoic acid methyl ester in 12 ml of dimethyl sulphoxide.

The mixture was stirred under nitrogen for 3 hours at 145°C and for 2 hours at 175°C. The mixture was then cooled, poured on to a small amount of ice, filtered (sodium carbonate) and the filtrate evaporated to dryness in a high vacuum (temperature less than 60°C). The residue was suspended in ethanol with warming and then filtered off under suction, there being obtained α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid sodium salt of melting point greater than 300°C.

Example 4.

A suspension of 12.7 g of α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - tolyl - benzoic acid methyl ester in a solution of 1.7 g of sodium hydroxide in 80 ml of water and 20 ml of ethanol was heated at reflux for 16 hours with stirring. The resulting solution was filtered while warm and adjusted to pH 6 with ca 40 ml of 1-N hydrochloric acid. The suspension was diluted with 300 ml of water and filtered, there being obtained α - (2,4 - diamino - 5 - pyrimidinyl)-2,6 - dimethoxy - p - toluic acid of melting point 264°—267°C (from methanol/water).

Example 5.

1.2 g of α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester were added to a solution of 200 mg of sodium metal in 200 ml of absolute isopropanol.

The resulting suspension was heated for 72 hours at 150°C and 5 atmospheres in a pressure tube. The solution was cooled and evaporated. The residual substance was suspended in a small amount of water, filtered off under suction and recrystallised from iso-

propanol, there being obtained α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid isopropyl ester of melting point 209°—213°C.

Example 6.

A solution of 0.4 g (17.4 mM) of sodium metal in 20 ml of absolute isopropanol was evaporated to dryness. The residue was dissolved in 10 ml of dimethyl sulphoxide. 2 g of α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester were added and the resulting mixture was stirred for 24 hours under nitrogen with the exclusion of moisture. After the addition of 30 ml of water, the precipitated α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid isopropyl ester was filtered off under suction and recrystallised from isopropanol.

Example 7.

1.6 g of α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester were dissolved in a solution of 20 mg of sodium metal in 250 ml of anhydrous butanol-(1). The mixture was boiled at reflux for 12 hours with the exclusion of moisture and subsequently filtered while hot. The filtrate was evaporated and the residue recrystallised from butanol-(1), there being obtained α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid butyl ester of melting point 186°—188°C.

Example 8.

2.0 g of α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester were added to a solution of ca 100 mg of sodium metal in 200 ml of absolute ethanol. The solution was heated at reflux for 48 hours and then filtered. The filtrate was concentrated to one quarter of its volume and then cooled. The precipitated α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid ethyl ester was filtered off under suction and recrystallised from ethanol; melting point 201°—202°C.

Example 9.

135 ml of a ca 15% diisobutyl - aluminium hydride solution in dioxane were added dropwise over a period of 30 minutes at 50°C under nitrogen and with the exclusion of moisture to a solution of 4.45 g of α - 2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester in 400 ml of absolute dioxane. The resulting suspension was stirred at 50°C for 1 hour. After cooling to 30°C, the mixture was treated with a mixture of 25 ml of methanol. 5 ml of water and 50 ml of dioxane and stirred at 50°C for a further 2 hours. The solid material was separated off and discarded. The filtrate was evaporated to dryness. After recrystallisation from ca 20 ml of methanol, the residue yielded 4 - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - 2,6 - dimethoxy - benzyl alcohol of melting point 227°—228°C.

Example 10.

A suspension of 3.18 g of α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester in 50 ml of dioxane was treated, while stirring, with 2.4 g of 3 - chloro - perbenzoic acid. After 5 minutes (oxidation agent no longer being detected), a further 1.2 g of 3 - chloro - perbenzoic acid were added. After 30 minutes, the brown-coloured solution (no peroxide; no oxidation agent) was evaporated to dryness and the residue treated with 200 ml of a mixture of chloroform/propanol/concentrated ammonia (80:20:2). The precipitated ammonium salt of the chlorobenzoic acid (ca 3.5 g) was separated, washed with chloroform and the solvent removed in vacuo. The residue (ca 3.0 g) was chromatographed on 90 g of silicagel using the aforementioned solvent system. The rapidly moving α - (2',4' - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester 3'-oxide was recrystallised from methanol; melting point 251°—253°C.

The slowly moving α - (2',4' - diamino - 5' - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester 1'-oxide (Rf 0.1) was recrystallised from methanol; melting point 258°—259°C (decomposition).

Example 11.

A solution of 735 mg of sodium in 100 ml of absolute alcohol was treated with 5.8 g of guanidine carbonate and 4.2 g of 4 - (3 - anilino - 2 - cyano - allyl) - 2,6 - diethoxy - benzoic acid ethyl ester and the mixture was boiled under reflux for 20 hours. The alcohol was evaporated in vacuo. 50 ml of water were added to the residue and, after stirring for 3 hours at 25°C, the α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - diethoxy - p - toluic acid ethyl ester was filtered off under suction, washed with water and recrystallised from alcohol; melting point 197°—199°C.

The starting material was prepared as follows:

A mixture of 29.7 g of 2,6 - dihydroxy - terephthalic acid, 228 g of potassium carbonate and 234 g of ethyl iodide in 500 ml of absolute dimethylformamide was stirred at 60°C for 18 hours with the exclusion of moisture. The solvent was removed in vacuo at 60°C and the residue treated with 750 ml of water. The resulting emulsion was extracted with two 700 ml portions of ethyl acetate. The ethyl acetate phases were washed with 600 ml of water, dried over magnesium sulphate and evaporated in vacuo. Recrystallisation of the residue from cyclohexane gave

2,6 - diethoxy - terephthalic acid diethyl ester of melting point 104°—105°C.

A solution of 24.8 g of 2,6 - diethoxy - terephthalic acid diethyl ester in 700 ml of alcohol was treated at 25°C while stirring during the course of 3 hours with 84 ml of 1-N sodium hydroxide. The solution was stirred for 70 hours at 25°C and then evaporated to dryness in vacuo at 40°C. The residue was dissolved in 400 ml of water and the aqueous solution extracted with 300 ml of ether. The ether phase was discarded and the aqueous phase acidified with concentrated hydrochloric acid. The precipitated 2,6 - diethoxy - terephthalic acid 1-monoethyl ester was filtered off under suction, washed with water, dried and recrystallised from ethyl acetate/cyclohexane; melting point 142°—144°C.

A solution of 20.9 g of 2,6 - diethoxy - terephthalic acid 1-monoethyl ester in 100 ml of thionyl chloride was boiled under reflux for 3 hours with the exclusion of moisture and then evaporated to dryness in vacuo. The residue was suspended in 300 ml of boiling petroleum ether (low-boiling range). After standing for 2 hours at 25°C, the 4 - chloroformyl - 2,6 - diethoxy - benzoic acid ethyl ester was filtered off under suction, washed with petroleum ether and dried; melting point 73°—74°C.

A mixture of 12 g of 4 - chloroformyl - 2,6 - diethoxy - benzoic acid ethyl ester, 1.4 g of palladium/barium sulphate catalyst (5%) and 0.2 ml of quinoline-sulphur regulator was heated to 120°C while gassing with nitrogen and stirring. Hydrogen was then conducted through the mixture at 120°C until the theoretical amount of hydrochloric acid had been liberated. The reduction was interrupted and the suspension cooled to 25°C while gassing with nitrogen. The catalyst was separated and the filtrate evaporated to dryness in vacuo, crude 2,6 - diethoxy - 4 - formyl - benzoic acid ethyl ester being obtained as a colourless oil. After recrystallisation from low-boiling petroleum ether, a sample yielded pure 2,6 - diethoxy - 4 - formyl - benzoic acid ethyl ester of melting point 45°—46°C.

A solution of 10.2 g of 2,6 - diethoxy - 4 - formyl - benzoic acid ethyl ester, 8.4 g of β - morpholino - propionitrile and 4.1 g of sodium ethylate in 40 ml of absolute dimethyl sulphoxide was stirred at 25°C for 20 hours. The solution was treated with 600 ml of water and extracted with two 500 ml portions of ethyl acetate. The ethyl acetate phases were washed twice with 200 ml of water each time, dried over magnesium sulphate and evaporated in vacuo. The residue was dissolved in 40 ml of alcohol. After standing at 4°C for 20 hours, the 4 - (2 - cyano - 3 - morpholino - allyl) - 2,6 - diethoxy - benzoic acid ethyl ester which crystallised out was filtered off under suction, washed with alcohol and dried; melting point 117°—119°C.

A solution of 3.7 g of 4 - (2 - cyano - 3 - morpholino - allyl) - 2,6 - diethoxy - benzoic acid ethyl ester, 1.4 g of aniline and 1.5 ml of concentrated hydrochloric acid in 100 ml of alcohol was boiled under reflux for 1 hour and then evaporated to dryness in vacuo. The residue was treated with 50 ml of water. After stirring at 25°C for 30 minutes, the 4 - (3 - anilino - 2 - cyano - allyl) - 2,6 - diethoxy - benzoic acid ethyl ester was filtered off under suction, washed with water, dried and recrystallised from methylene chloride/alcohol; melting point 178°—179°C.

Example 12.

A mixture of 1.94 g of 4 - (2 - cyano - 3 - morpholino - allyl) - 2,6 - diethoxy - benzoic acid ethyl ester, 3.6 g of guanidine carbonate and 1.36 g of sodium ethylate in 20 ml of absolute dimethyl sulphoxide was stirred at 120°C for 20 hours. After the addition of 200 ml of water, the mixture was extracted with two 200 ml portions of ethyl acetate. The ethyl acetate phases were washed twice with 50 ml of water each time, dried over magnesium sulphate and evaporated in vacuo. The residue was chromatographed on 40 g of solocagel (Merck) using ethyl acetate/methanol (4:1), α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - diethoxy - p - toluic acid ethyl ester of melting point 197°—199°C being obtained.

Example 13.

A Grignard reagent prepared from 53.5 g of magnesium and 284 g of methyl iodide in 500 ml of absolute ether was treated, while stirring and cooling with ice, over a period of 2 hours with a solution of 36 g of α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - diethoxy - p - toluic acid ethyl ester in 2 litres of absolute tetrahydrofuran. The resulting suspension was boiled under reflux for 20 hours. The mixture, cooled to 25°C, was carefully decomposed with ice and then 3 litres of water and 2-N sodium hydroxide were added until a strong alkaline reaction was obtained. The resulting precipitate was filtered off under suction and the filtrate extracted with two 5 litre portions of ethyl acetate. The ethyl acetate phases were washed with two 2 litre portions of water, dried over magnesium sulphate and evaporated to dryness in vacuo. The residue was dissolved in 2 litres of absolute tetrahydrofuran and again reacted, in the manner described earlier in this Example, with a Grignard reagent prepared fom 26.7 g of magnesium, 142 g of methyl iodide and 250 ml of absolute ether. The product obtained after working-up was chromatographed on 400 g of silicagel (Merck) using ethyl acetate/methanol (3:1), there being obtained 4 - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - 2,6 - diethoxy - α,α - dimethyl - benzyl alcohol of melting point 217°—218°C after recrystallisation from methanol.

Example 14.

A suspension of 8.0 g of α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluamide in 25 ml of dry pyridine was treated dropwise at 20°—30°C with 4.0 g of phosphorus oxychloride. After stirring for 3 hours at room temperature, the mixture was poured into 150 ml of water, the precipitated α-(2,4-diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluonitrile was filtered off under suction, washed with water and recrystallised from dimethylformamide/methanol; melting point 270°—272°C.

The starting material was prepared as follows:

A solution of 195 g of 2,6 - dimethoxy - 4 - methyl - benzamide in 2.5 litres of water and 1.7 litres of pyridine was treated portionwise while stirring at 80°C over a period of 1 hour with 630 g of potassium permanganate. The mixture was boiled under reflux for 2 hours. The manganese dioxide was separated, washed with 1 litre of hot water and the filtrate evaporated to dryness in vacuo. The residue was taken up in 1 litre of water, the starting material filtered off under suction and the filtrate treated with concentrated hydrochloric acid until a strong acidic reaction was obtained. The precipitated 3,5 - dimethoxy - terephthalamic acid was separated, washed with water and dried; melting point greater than 300°C.

A solution of 50 g of 3,5 - dimethoxy - terephthalamic acid in 500 ml of methanol was saturated with hydrogen chloride gas, boiled under reflux for 3 hours with the introduction of further hydrogen chloride and then evaporated to drynes in vacuo. The residue was cautiously shaken with 200 ml of a 5% sodium bicarbonate solution, the solid material was filtered off under suction, washed with water and recrystallised from methanol. The 3,5 - dimethoxy - terephthalamic acid methyl ester melts at 259°—261°C.

A suspension of 2.4 g of sodium hydride (50% dispersion in oil) and 7.05 g of dimethylsulphone in 18 ml of absolute dimethyl sulphoxide was stirred at 50°C for 2 hours under nitrogen and with the exclusion of moisture. The heating was interrupted and 5.95 g of 3,5 - dimethoxy - terephthalamic acid methyl ester were added, the temperature rising to 65°C. The mixture was stirred for a further hour at room temperature, diluted with 100 ml of water, the aqueous solution extracted twice with 50 ml of ethyl acetate each time, filtered over carbon and adjusted to pH 6—7 with glacial acetic acid. The precipitated 2,6 - dimethoxy - 4 - (methylsulphonyl - acetyl) - benzamide was filtered off under suction, washed with water and recrystallised from dimethylformamide/ether; melting point 228°—230°C.

A suspension of 37 g of 2,6 - dimethoxy - 4 - (methylsulphonyl - acetyl) - benzamide in 50 ml of ethanol and 155 ml of water was treated with a solution of 1.55 g of sodium borohydride in 30 ml of water (with the addition of 0.1 g of sodium hydroxide). The mixture was stirred for a further 2 hours at room temperature, cooled with ice and the solid material filtered off under suction. After recrystallisation from dimethylformamide/ethanol, the 4 - [1 - hydroxy - 2 - (methylsulphonyl - ethyl)] - 2,6 - dimethoxy - benzamide melted at 258°C with decomposition.

A mixture of 3.1 g of sodium methylate, 16 g of 4 - [1 - hydroxy - 2 - (methylsulphonyl - ethyl)] - 2,6 - dimethoxy - benzamide and 8.2 g of β - anilino - propionitrile in 35 ml of absolute dimethyl sulphoxide was stirred at 50°C for 5 hours under nitrogen and with the exclusion of moisture. The solution was poured into 400 ml of water and the resulting emulsion extracted with three 200 ml portions of ethyl acetate. The ethyl acetate phases were washed with water, dried over sodium sulphate and evaporated in vacuo. The residue was recrystallised from dimethylformamide/water. The 4 - (3 - anilino - 2 - cyano - allyl) - 2,6 - dimethoxy - benzamide melted at 226°—228°C.

A solution of 0.83 g of sodium in 55 ml of absolute ethanol was treated with 3.52 g of guanidine hydrochloride and 4.1 g of 4 - (3 - anilino - 2 - cyano - allyl) - 2,6 - dimethoxy - benzamide and the resulting mixture was boiled for 20 hours under nitrogen and with stirring. The mixture was diluted with 100 ml of water and the ethanol removed in vacuo. The precipitated α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluamide was filtered off under suction, washed with water and recrystallised from dimethylformamide/methanol; melting point 288°—290°C.

Example 15.

A suspension of 1.0 g of N - [4 - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - benzyl] - acetamide in 30 ml of 1-N hydrochloric acid was heated at 100°C for 15 hours. A clear solution resulted and the mixture was subsequently evaporated to dryness in vacuo. The residue was disolved in a small amount of water, the solution made alkaline with potassium carbonate and the precipitated 2,4 - diamino - 5 - (4 - aminomethyl - 3,5 - dimethoxy - benzyl) - pyrimidine was converted into the maleate of melting point 176°—178°C (decomposition).

Example 16.

A solution of 0.53 g of sodium in 36 ml of absolute ethanol was treated with 2.6 g of guanidine hydrochloride and 3.4 g of N - [4 - (3 - anilino - 2 - cyano - allyl) - 2,6 - dimethoxy - benzyl] - acetamide and the mixture was boiled for 20 hours under nitrogen and with stirring. The ethanol was removed

under reduced pressure, the residue taken up in water, filtered off under suction, washed with water and recrystallised from methanol. The N - [4 - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - benzyl] - acetamide melted at 218°—220°C.

The starting material was prepared as follows:

A mixture of 20 g of 3,5 - dimethoxy - terephthalamic acid and 100 ml of thionyl chloride was boiled under reflux for 1 hour, a clear solution resulting. The mixture was evaporated to dryness under reduced pressure, the residue dissolved in benzene, the benzene distilled off, the residue again dissolved in benzene and this solution added dropwise to 400 ml of methanol. The mixture was boiled under reflux for 1 hour, evaporated to dryness, the residue dissolved in benzene, the benzene solution washed with water, sodium bicarbonate solution and water, dried and evaporated. By recrystallisation of the residue from methanol, there was obtained 4 - cyano - 3,5 - dimethoxy - benzoic acid methyl ester of melting point 151°—153°C.

30 g of 4 - cyano - 3,5 - dimethoxy - benzoic acid methyl ester in 1500 ml of methanol and 150 ml of 1-N hydrochloric acid were hydrogenated in the presence of 10 g of palladium-on-carbon (10%) at room temperature and atmospheric pressure. 2 mols of hydrogen were taken up in ca 5 hours. The solution was filtered from the catalyst, the filtrate evaporated to dryness, the residue taken up in a small amount of water, the solution filtered, saturated with solid potassium carbonate and extracted with benzene. From the benzene phase there was obtained 4 - aminomethyl - 3,5 - dimethoxy - benzoic acid methyl ester which, after recrystallisation from high-boiling petroleum ether, melted at 81°—83°C.

9.0 g of 4 - aminoethyl - 3,5 - dimethoxy - benzoic acid methyl ester dissolved in 30 ml of glacial acetic acid were treated dropwise with 4.1 g of acetic anhydride and the mixture was warmed on a steam-bath for 30 minutes. The acetic acid was distilled off and the residue recrystallised from methanol. The 4 - acetylaminomethyl - 3,5 - dimethoxy - benzoic acid methyl ester melted at 184°C.

A suspension of 2.9 g of sodium hydride (50% dispersion in oil) and 3.8 g of dimethylsulphone in 20 ml of absolute dimethyl sulphoxide was stirred at 50°C for 2 hours under a nitrogen atmosphere and with the exclusion of moisture. The heating was interrupted and 5.34 g of 4 - acetylaminomethyl - 3,5 - dimethyl - benzoic acid methyl ester were added, the temperature rising to 63°C. The mixture was stirred at room temperature for a further 2 hours and then diluted with 200 ml of water. The aqueous solution was extracted twice with 50 ml of ethyl acetate each time, filtered over carbon, adjusted to pH 6—7 with glacial acetic acid and stored overnight in a refrigerator. The precipitated N - [2,6 - dimethoxy - 4 - (methylsulphonyl - acetyl) - benzyl] - acetamide was filtered off under suction, washed with water and recrystallised from methanol/water (50:50); melting point 233°—235°C. The yield was 6.4 g.

A suspension of 9.5 g of N - 2,6 - dimethoxy - 4 - (methyl - sulphonyl - acetyl) - benzyl] - acetamide in 120 ml of ethanol and 120 ml of water was treated with a solution of 2.4 g of sodium borohydride in 30 ml of water (with the addition of 0.1 g of sodium hydroxide). The mixture was stirred for a further 3 hours at room temperature, cooled with ice, poured into 150 ml of water and the solid material filtered off under suction. After recrystallisation from methanol, the N - [p - [1 - hydroxy - 2 - (methylsulphonyl-ethyl)] - 2,6 - dimethoxy - benzyl] - acetamide melted at 190°C.

A mixture of 0.82 g of sodium methylate, 3.28 g of N - [p - [1 - hydroxy - 2 - (methylsulphonyl - ethyl)] - 2,6 - dimethoxy - benzyl] - acetamide and 2.2 g of β - anilino - propionitrile in 13 ml of absolute dimethyl sulphoxide was stirred at 50°C for 5 hours under nitrogen and with the exclusion of moisture. After cooling, the solution was poured into 60 ml of water and the resulting emulsion extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried over sodium sulphate and evaporated. The residue was recrystallised from methanol. The N - [4 - (3 - anilino - 2 - cyano - allyl) - 2,6 - dimethoxy - benzyl] - acetamide melted at 216°C.

Example 17.

4.6 g (96 mM) of sodium hydride (ca 50% suspension) were added to a solution of 4.5 g of dimethylsulphone in 10 ml of absolute dimethyl sulphoxide and the mixture was stirred at 60°C for 2 hours. 5.8 g of α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - diethoxy - p - toluoyl - benzoic acid ethyl ester were then added in three portions, the temperature rising to 65°C. The mixture was stirred at 60°C for a further 15 minutes and, after cooling with ice-water, treated with ca 150 ml of water. The turbid solution was washed three times with 50 ml of benzene each time and the benzene extracts were discarded. The aqueous phase was adjusted to pH 7—8 with 10 ml of concentrated hydrochloric acid, the precipitated 4' - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - 2',6' - diethoxy - 2 - methylsulphonyl - acetophenone filtered off under suction and dried in a high vacuum at 50°C. The melting point after recrystallisation from water was 206°—207°C.

Example 18.

A suspension of 5.8 g of 4' - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - 2',6' -

diethoxy - 2 - methylsulphonyl - acetophenone in 50 ml of 20% aqueous tetrahydrofuran was reduced with 1 g of aluminium amalgam at 65°C for 4 hours. Aluminium shavings were immersed in a 2% $HgCl_2$ solution, rinsed with methanol and used immediately for the reduction.) The mixture was adjusted to pH 9 with 5% sodium hydroxide and extracted with five 50 ml portions of ethyl acetate. There was obtained a crude product which, after column chromatography [200 g of silicagel; eluant : chloroform/n-propanol/concentrated ammonium hydroxide (80:20:1)], yielded 4' - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - 2',6' - diethoxy - acetophenone of melting point 229°—231°C (from ethanol).

Example 19.

11.5 g (25 mM) of sodium hydride (ca 50% suspension) were added to a solution of 8.8 g of dimethylsulphone in 20 ml of dimethyl sulphoxide dried over molecular sieves. The mixture was stirred at 60°C for 2 hours under nitrogen. At this temperature (the heating bath being removed), 10 g of α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester were added portionwise, the temperature rising to 70°—75°C. The mixture was stirred at 60°C for a further 15 minutes and then cooled. The mixture was then treated with 250 ml of water while cooling and under a stream of nitrogen. The turbid solution was washed with three 50 ml portions of benzene (the benzene extracts being discarded), adjusted to pH 7—8 with concentrated hydrochloric acid and extracted six times with 200 ml of ethyl acetate each time. The combined extracts were dried over magnesium sulphate and concentrated and the residue was kept under a high vacuum for 5 hours. There was obtained 4' - [2,4 - diamino - 5 - pyrimidinyl) - methyl] - 2',6' - dimethoxy - 2 - methylsulphonyl - acetophenone of melting point 223°—225°C.

A sample, dissolved in water and acidified with concentrated hydrochloric acid, yielded after recrystallisation from methanol, 4 - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - 2',6' - dimethoxy - 2 - methylsulphonyl - acetophenone hydrochloride of melting point greater than 300°C.

Example 20.

A solution of 7.0 g of 4' - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - 2',6' - dimethoxy - 2 - methylsulphonyl - acetophenone in 80 ml of 20% aqueous tetrahydrofuran was reduced with 1 g of aluminium amalgam at 40°C for 1 hour. The mixture was filtered, the filtrate concentrated to about one third of its volume and adjusted to pH 9 with 4-N sodium hydroxide. The precipitated product was taken up in ethyl acetate. The ethyl acetate extract was dried over magnesium sulphate and evaporated. The residue was recrystallised from methanol and gave 4' - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - 2',6' - dimethoxy - acetophenone of melting point 282°—285°C.

Example 21.

500 mg of sodium borohydride were added portionwise while stirring and over a period of 30 minutes to a suspension of 1 g of 4' - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - 2',6' - diethoxy - 2 - methylsulphonyl - acetophenone in a mixture of 25 ml of ethanol and 10 ml of water. A clear solution resulted initially and, after stirring for a further 30 minutes, 4 - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - 2,6 - diethoxy - α - (methylsulphonyl - methyl) - benzyl alcohol crystallised out; melting point 205°—206°C after recrystallisation from methanol.

Example 22.

A solution of 302 mg of 4' - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - 2',6' - dimethoxy - acetophenone in 30 ml of methanol was diluted with 6 ml of water and one drop of 1-N sodium hydroxide was added thereto. 200 mg of sodium borohydride were then added in 50 mg portions over a period of 3 hours at 40°C. About half of the solvent was distilled off in vacuo. The precipitated 4 - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - 2,6 - dimethoxy - α - methyl - benzyl alcohol was filtered off under suction and then recrystallised from methanol; melting point 280°—285°C (decomposition).

Example 23.

4.0 g of 4 - (1 - hydroxy - ethyl) - 3,5 - dimethoxy - α - (methoxy - methylene) - hydrocinnamic acid nitrile were added to a guanidine solution in methanol prepared from 0.34 g of sodium metal in 40 ml of methanol and 1.38 g of guanidine hydrochloride. The mixture was boiled at reflux for 18 hours. The solvent was evaporated at normal pressure and the semi-solid residue purified by column chromatography [100 g of silicagel; eluant: chloroform / n - propanol / concentrated ammonium hydroxide (80:20:1)]. After concentration of the fractions containing the product and recrystallisation of the residue from methanol, there was obtained 4 - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - 2,6 - dimethoxy - α - methyl - benzyl alcohol of melting point 280°—282°C.

The starting material was prepared as follows:

3 g (0.06 M) of a ca 50% suspension of sodium hydride were added to a solution of 8.5 g of dimethylsulphone in 15 ml of dimethyl sulphoxide and the mixture was stirred at 60°C for 2 hours under nitrogen. A solution of 9 g of 2,6 - dimethoxy - 4 - diethoxymethyl - benzoic acid methyl ester in 5 ml of dimethyl sulphoxide was then added drop-

wise and the mixture was stirred at 65°C for a further 30 minutes. After cooling, the mixture was dissolved up while cooling with 100 ml of water and extracted with five 50 ml portions of ether. The combined ether extracts were dried over magnesium sulphate, evaporated to dryness and the residue, 2,6 - dimethoxy - 4 - diethoxymethyl - methylsulphonyl - acetophenone was used directly without further working-up.

A solution of 8.8 g of the foregoing sulphone in 80 ml of 10% aqueous tetrahydrofuran was reduced with 0.8 g of amalgamated aluminium shavings at 50°C for 2 hours. After this time no sulphone could be detected. The suspension was filtered, the filtrate concentrated to about two thirds of its volume and extracted with five 50 ml portions of ether. After drying the ether extracts and evaporation of the solvent, there was obtained 4 - diethoxymethyl - 2,6 - dimethoxy - acetophenone.

1 g of sodium borohydride was added in several portions at room temperature while stirring and over a period of 4 hours to a solution of 4 g of 4 - diethoxymethyl - 2,6 - dimethoxy - acetophenone in 20 ml of 30% methanol and one drop of 4-N sodium hydroxide. The mixture was stirred for a further 1 hour, concentrated to about one third of its volume and diluted with 30 ml of water. The resulting suspension was acidified to pH 1 with 2-N hydrochloric acid, covered with 50 ml of ether and stirred at room temperature for 1 hour. The ether phase was then separated, dried over magnesium sulphate and evaporated. After crystallisation from ether, the residue yielded 4 - (1 - hydroxy - ethyl) - 3,5 - dimethoxy - benzaldehyde of melting point 95°—96°C.

1.94 g of β - methoxy - propionitrile and 4.0 g of 4 - (1 - hydroxy - ethyl) - 3,5 - dimethoxy - benzaldehyde were dissolved in a solution of 0.45 g of sodium in 20 ml of methanol and the mixture was boiled at reflux for 24 hours. After evaporation of the solvent, the residue was taken up in 50 ml of benzene and 10 ml of water. The benzene phase was separated and washed several times with water. The resulting 4 - (1 - hydroxy - ethyl) - 3,5 - dimethoxy - α - (methoxy - methylene) - hydrocinnamic acid nitrile, a yellowish oil, was used in the process described in the first paragraph of this Example after evaporation of the benzene.

A sample was purified by preparative thin-layer chromatography and gave 4 - (1 - hydroxy - ethyl) - 3,5 - dimethoxy - α - (methoxy - methylene) - hydrocinnamic acid nitrile as a colourless oil which becomes crystalline with time, the crystals melting at below 30°C.

Example 24.

In a manner analogous to that described in the first paragraph of Example 2, from 3.5 g of α - (dimethoxy - methyl) - 3,5 - dimethoxy - 4 - (1 - hydroxy - propyl) - hydrocinnamic acid nitrile, 2.29 g (24 mM) of guanidine hydrochloride, 0.56 g of sodium and 35 ml of methanol there was obtained 4 - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - α - ethyl - 2,6 - dimethoxy - benzyl alcohol of melting point 235°—238°C (from methanol).

The starting material was prepared as follows:

2.74 g of β - methoxy - propionitrile and 4.8 g of 4 - (1 - hydroxy - propyl) - 3,5 - dimethoxy - benzaldehyde were dissolved in a solution of 0.18 g of sodium metal in 50 ml of absolute methanol and the resulting mixture was boiled at reflux for 48 hours. The mixture was evaporated and the residue taken up in 50 ml of benzene and 10 ml of water. The aqueous phase was washed twice with 20 ml of benzene each time. The combined benzene extracts were dried and evaporated. The residue, a yellowish oil, was used in the process described in the first paragraph of this Example without further purification.

A sample was purified by preparative thin-layer chromatography on silicagel using ether as the eluant, there being obtained α - (dimethoxy - methyl) - 3,5 - dimethoxy - 4 - (1 - hydroxy - propyl) - hydrocinnamic acid nitrile as a colourless oil.

Example 25.

2.3 g of guanidine hydrochloride were added to a solution of 0.62 g of sodium metal in 50 ml of methanol and the suspension was stirred for 30 minutes. The sodium chloride was filtered off under suction and washed with a small amount of cold methanol. The filtrate was added to a solution of 5.0 g of α - (dimethoxy - methyl) - 3,5 - dimethoxy - 4 - (methoxy - methyl) - hydrocinnamic acid nitrile in 20 ml of methanol and the mixture was boiled at reflux for 2 hours. Methanol was then distilled off via a water-separator while increasing the internal temperature to 80°C. 25 ml of isopropanol were added to the residue and the isopropanol was distilled off over a period of 2 hours. The residue was then subjected to chromatography [100 g of silicagel; eluant: chloroform/n-propanol/ammonia (80:20:1)], there being obtained 2,4 - diamino - 5 - [3,5 - dimethoxy - 4 - (methoxy - methyl) - benzyl] - pyrimidine of melting point 221—223°C (from methanol).

The starting material was prepared as follows:

29.8 g of 2,6 - dimethoxy - 4 - (α,α - diethoxy - methyl) - benzoic acid methyl ester were dissolved in 250 ml of absolute benzene and treated at 25°—40°C with 230 ml of a ca 20% solution of diisobutyl-aluminium

hydride in toluene. The homogeneous mixture was stirred at room temperature for 3 hours and then dissolved up with a solution of 10 ml of water, 25 ml of methanol and ca 10 ml of benzene while cooling in such a manner that the temperature did not exceed 40°C. The resulting suspension was stirred for a further 30 minutes, the aluminium hydroxide filtered off under suction, washed with benzene and the filtrate evaporated to dryness. There was obtained 2,6 - dimethoxy - 4 - (α,α - diethoxy methyl - benzyl alcohol as a colourless viscous oil.

After treatment of the foregoing oil with 20 ml of 1-N hydrochloric acid and crystallisation from benzene, there was obtained crystalline α - hydroxy - 3,5 - dimethoxy - p - tolualdehyde of melting point 128°—129°C (sublimation).

A solution of 20 g of 2,6 - dimethoxy - 4 - (α,α - diethoxy methyl) - benzyl alcohol in 40 ml of absolute ether was added dropwise to a suspension of 2.35 g (0.07 M) of sodium hydride (55%) in 40 ml of absolute ether. The mixture was stirred under nitrogen at room temperature for 1 hour, then treated with 40 g (0.28 M) of methyl iodide and stirred at reflux for 22 hours. The solvent and excess methyl iodide were distilled off, the residue treated with 100 ml of 1-N hydrochloric acid at 25°C over a period of 15 minutes and the resulting aldehyde was taken up in ether. Recrystallisation from benzene/n-pentane yielded α,3,5 - trimethoxy - p - tolualdehyde of melting point 72°—76°C.

2.45 g of β - methoxy - propionitrile and 5 g of α,3,5 - trimethoxy - tolualdehyde were dissolved in a solution of 0.25 g of sodium metal in 20 ml of absolute methanol and the resulting mixture was boiled at reflux for 48 hours. No aldehyde could be detected after this time. After evaporation of the solvent, the residue was taken up in 50 ml of benzene and 15 ml of water, the benzene phase separated and washed several times with water, dried over magnesium sulphate and evaporated. There was obtained a yellowish oil which was used in the process described in the first paragraph of this Example without further working-up.

An analytical sample was purified by chromatography on silicagel using ether as the eluant, there being obtained α - (dimethoxy - methyl) - 3,5 - dimethoxy - 4 - (methoxy - methyl) - hydrocinnamic acid nitrile as a colourless crystalline substance of melting point ca 30°C.

Example 26.

A suspension of 11.3 g of N - [2 - amino - 5 - [4 - (1 - hydroxy - 1 - methyl - ethyl) - 3,5 - dimethoxy - benzyl] - 4 - pyrimidinyl] - acetamide in 40 ml of 10% methanolic potassium hydroxide was boiled at reflux for 1 hour and then cooled to ca 10°C. The crystals were filtered off under suction and washed with a small amount of methanol. After crystallisation from methanol, there was obtained 4 - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - 2,6 - dimethoxy - α,α - dimethyl - benzyl alcohol of melting point 248°—250°C.

The starting material was prepared as follows:

5 g of α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester were added portionwise to 10 ml of hot (95°C) acetic anhydride. The resulting solution was stirred for a further 30 minutes at 95°C and then treated with 30 ml of toluene and cooled. The α - (2,4 - diacetamido - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester was filtered off under suction and recrystallised from methanol; melting point 183°—185°C.

A solution of 2.5 g of α - (2,4 - diacetamido - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester in 200 ml of absolute tetrahydrofuran was added dropwise over a period of 30 minutes to a methylmagnesium iodide solution prepared from 2.4 g of magnesium and 14.5 g of methyl iodide in 100 ml of ether. The resulting suspension was stirred at 40°C for 24 hours. The mixture was treated with 20 ml of water, the organic phase separated and washed with a small amount of 4-N sodium hydroxide and water, dried over magnesium sulphate and evaporated. The crude product thus-obtained, a yellowish oil, was used in the process described in the first paragraph of this Example without further working-up.

A sample was subjected to chromatographic purification on silicagel using chloroform/n-propanol/concentrated ammonia (80:20:1) as the eluant, there being obtained N - [2 - amino - 5 - [4 - (1 - hydroxy - 1 - methyl - ethyl) - 3,5 - dimethoxy - benzyl] - 4 - pyrimidinyl] - acetamide of melting point 214°—216°C (from methanol).

Example 27.

21.1 g of guanidine hydrochloride were added to a solution of 5.1 g of sodium metal in 300 ml of absolute methanol and the resulting suspension was heated at reflux for 15 minutes. After cooling, the sodium chloride was filtered off under suction and washed with a small amount of cold methanol. 51.4 g of 4 - (1 - hydroxy - 1 - methyl - ethyl) - 3,5 - dimethoxy - α - (methoxy - methylene) - hydrocinnamic acid nitrile were dissolved in the filtrate and the mixture was boiled at reflux for 18 hours. After cooling, the mixture was concentrated in vacuo, the residue suspended in ca 50 ml of methanol while warming, again cooled, the solid material filtered off under suction and washed with cold methanol. Crystallisation from methanol gave 4 - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - 2,6 - dimethoxy - α,α - dimethyl - benzyl alcohol of melting point 248°—250°C.

The starting material was prepared as follows:

A solution of 22.4 g of 2,6 - dimethoxy - 4 - formyl - benzoic acid methyl ester, 17.8 g of orthoformic acid ethyl ester and 0.5 ml of concentrated hydrochloric acid in 100 ml of absolute ethanol was boiled at reflux for 2 hours. The mixture was concentrated under reduced pressure and yielded 2,6 - dimethoxy - 4 - (α,α - diethoxy - methyl) - benzoic acid methyl ester.

A methylmagnesium iodide solution was prepared from 21.6 g of magnesium and 62 ml of methyl iodide in 800 ml of ether. 90 g of 2,6 - dimethoxy - 4 - (α,α - diethoxy - methyl) - benzoic acid methyl ester in 150 ml of ether were added dropwise to this Grignard solution at room temperature. After the reaction had died down, the mixture was boiled at reflux for a further 3 hours. After cooling, the suspension was treated with 50 ml of water, 50 ml of 4-N sodium hydroxide were added, the ether phase was separated and washed with 10 ml of 4-N sodium hydroxide. The aqueous-alkaline solution was extracted with five 200 ml portions of ether and the combined ether extracts dried over sodium sulphate and evaporated. The residue was shaken well for 10 minutes with 250 ml of 1-N hydrochloric acid and taken up in ca 250 ml of ether. The ether solution was washed with water, dried over magnesium sulphate and concentrated. Crystallisation from ether/petroleum ether yielded 4 - (1 - hydroxy - 1 - methyl - ethyl) - 3,5 - dimethoxy - benzaldehyde of melting point 52°—53°C.

From 1.5 g of sodium in 500 ml of methanol, 20.8 g of β - methoxy - propionitrile and 50.0 of 4 - (1 - hydroxy - 1 - methyl - ethyl) - 3,5 - dimethoxy - benzaldehyde there was obtained, by heating under reflux for 48 hours and working-up, 4 - (1 - hydroxy - 1 - methyl - ethyl) - 3,5 - dimethoxy - α - (methoxy - methylene) - hydrocinnamic acid nitrile as a yellow oil.

An analytical sample was purified by chromatography on silicagel using ether as the eluant; melting point ca 55°C.

Example 28.

2.96 g of guanidine hydrochloride were added to a solution of 0.73 g of sodium metal in 45 ml of methanol and the resulting suspension was boiled at reflux for 15 minutes. After cooling, the sodium chloride was filtered off under suction and 8 g of 4 - (1 - hydroxy - 1 - ethyl - propyl) - 3,5 - dimethoxy - α - (methoxy - methylene) - hydrocinnamic acid nitrile were dissolved in the filtrate. The mixture was boiled at reflux for 24 hours, the solvent evaporated off at normal pressure and the residue heated at 110°C for 15 minutes. The semi-solid mixture was purified by column chromatography [200 g of silicagel; eluant: chloroform/n-propanol/concentrated ammonia (80:20:1)] and yielded, after recrystallisation from methanol, 4 - [(2,4 - diamino - 5 - pyrimidinyl) - methyl] - α,α - diethyl - 2,6 - dimethoxy - benzyl alcohol of melting point 160°—161°C.

The starting material was prepared as follows:

A Grignard solution was prepared from 2.16 g of magnesium shavings and 10.3 ml of ethyl iodide in 280 ml of absolute ether. 9 g of 2,6 - dimethoxy - 4 - (diethoxy - methyl) - benzoic acid methyl ester were added to this Grignard solution, the temperature rising to ca 32°C. The mixture was boiled at reflux for 2 hours and then treated with 15 ml of water and 50 ml of 4-N sodium hydroxide. The aqueous phase was separated and washed five times with 15 ml of ether each time. The combined ether extracts were washed with water and concentrated to 100 ml. The ether solution was stirred overnight at room temperature with 25 ml of 1-N hydrochloric acid. The ether phase was separated, washed with water, dried over magnesium sulphate and concentrated. The residue, a colourless oil (7.7 g), was a mixture of two substances which were separated by column chromatography on 650 g of silicagel using benzene/ether (3:1) as eluant.

The substance with R_f 0.45 in the foregoing system was a colourless oil and was identified as 4 - (1 - hydroxy - 1 - ethyl - propyl) - 3,5 - dimethoxy - benzaldehyde.

The slower running compound (R_f 0.30) was a colourless oil and was identified as 4 - (1 - hydroxy - propyl) - 3,5 - dimethoxy - benzaldehyde.

8 g of 4 - (1 - hydroxy - 1 - ethyl - propyl) - 3,5 - dimethoxy - benzaldehyde and 5.4 g of β - methoxy - propionitrile were added to a solution of 0.44 g of sodium metal in 40 ml of absolute methanol. The resulting yellow-brown solution was boiled at reflux for 18 hours. The mixture was then concentrated and the residue taken up in 250 ml of ether and 100 ml of water. The ether phase was washed three times with 50 ml of water each time, dried over magnesium sulphate, evaporated and dried in a high vacuum at 40°C for 8 hours. The thus-obtained crude product was used in the process described in the first paragraph of this Example without further purification.

A sample was purified by preparative thin-layer chromatography, there being obtained 4 - (1 - hydroxy - 1 - ethyl - propyl) - 3,5 - dimethoxy - α - (methoxy - methylene) - hydrocinnamic acid nitrile as a colourless oil.

Example 29.

A solution of 40 mg of $HgCl_2$ in 1 ml of water and 700 mg of zinc powder was added to a solution of 0.9 g of α - (2,4 - diamino - 6 - chloro - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester in 12 ml

of glacial acetic acid and the mixture was boiled at reflux and stirred overnight. The mixture was filtered while hot, the zinc powder washed on the filter with 6 ml of 90% acetic acid and the combined filtrates were made alkaline while cooling with 20 ml of concentrated ammonium hydroxide. The precipitated α - (2,4 - diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester was filtered off under suction and recrystallised from methanol; melting point 250°—251°C.

The starting material was manufactured as follows:

A mixture of 11.2 g of 2,6 - dimethoxy - 4 - formyl - benzoic acid methyl ester, 6.3 g of cyanoacetic acid ethyl ester and three drops of piperidine was heated in an open vessel while stirring to 120°C and stirred at this temperature for a further 15 minutes. The residue was recrystallised from ethyl acetate and yielded α - cyano - 3,5 - dimethoxy - 4 - methoxycarbonyl - cinnamic acid ethyl ester of melting point 142°—144°C.

A solution of 10.6 g of α - cyano - 3,5 - dimethoxy - 4 - methoxy - carbonyl - cinnamic acid ethyl ester in 500 ml of ethanol was hydrogenated in the presence of 0.5 g of palladium-on-carbon (5%) at room temperature and 760 Torr. After the uptake of an equivalent of hydrogen (810 ml), the hydrogenation was interrupted. The catalyst and partially precipitated product were filtered off under suction and washed on the filter with benzene. The filtrate was evaporated to dryness. The residue was recrystallised from ethyl acetate and yielded α - cyano - 3,5 - dimethoxy - 4 - methoxycarbonyl - dihydrocinnamic acid ethyl ester of melting point 119°—121°C.

8 g of α - cyano - 3,5 - dimethoxy - 4 - methoxycarbonyl - dihydrocinnamic acid ethyl ester were dissolved in a solution of 0.7 g of sodium metal in 80 ml of absolute ethanol and the mixture was treated with an ethanolic solution of guanidine prepared from 0.7 g of sodium in 100 ml of ethanol and 2.7 g (0.028 M) of guanidine hydrochloride. The mixture was boiled at reflux for 2 hours and then evaporated to dryness. The residue was dissolved in 90 ml of hot water, filtered and acidified to pH 4 with glacial acetic acid. After recrystallisation from methanol, the precipitated product gave α - (2,4 - diamino - 6 - hydroxy - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester of melting point 224°—226°C.

2.4 g of N,N - dimethyl - aniline were added dropwise while stirring to a suspension of 3.4 g of α - (2,4 - diamino - 6 - hydroxy - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester in 25.6 g of phosphorus oxychloride. The resulting mixture was brought to the boiling temperature in the course of 1 hour and then boiled at reflux for 4 hours. Then two thirds of the phosphorus oxychloride were distilled off under reduced pressure, the residue poured on to 80 g of ice while stirring and left to stand for two days at room temperature. The suspension was treated with 38 ml of 25% aqueous ammonia, the temperature not exceeding 20°C. After 2 hours, the solid material was filtered off under suction, rinsed with a small amount of water in a flask and separated from the N,N - dimethyl - aniline with steam. After cooling, the compound in suspension was filtered off under suction and taken up in ethyl acetate. The solution was dried over magnesium sulphate and the solvent evaporated. The dark residue (1.6 g) was purified by column chromatography on 60 g of silicagel (Merck) using chloroform/n-propanol/25% ammonia (80:20:1) as the eluant, there being obtained α - (2,4 - diamino - 6 - chloro - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester of melting point 228°—229°C (from methanol).

The following Example illustrates a typical pharmaceutical preparation containing one of the benzylpyrimidine derivatives provided by the invention:

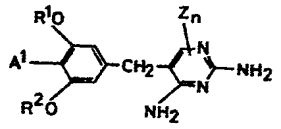
Example A.

Tablet formulation:

Methyl α-(2,4-diamino-5-pyrimidinyl)-2,6-dimethyl-p-toluate	80 mg
Sulphamethoxazole	400 mg
Corn starch	114 mg
Talc	5 mg
Magnesium stearate	1 mg
Total weight	600 mg

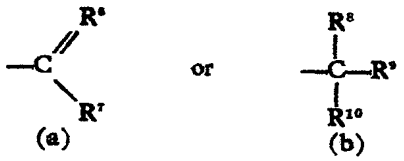
WHAT WE CLAIM IS:—

1. Compounds of the general formula



(I)

wherein R^1 and R^2 each represent an alkyl or alkenyl group, Z represents an oxygen atom bonded to one of the cyclic nitrogen atoms, n stands for zero or 1 and A^1 represents a trifluoromethyl group or a group of the formula



(a) (b)

in which R^8 represents an oxygen atom and

R^7 represents a hydrogen atom or an alkyl or alkoxy group; or R^6 represents a hydroxyimino group and R^7 represents an alkyl group; or R^6 together with R^7 and the carbon atom to which they are attached represent a nitrilo group; R^8 and R^9 each represent a hydrogen atom or an alkyl group and R^{10} represents a hydroxy, alkoxy or $-N(R^3)(R^4)$ group; or R^9 and R^{10} each represent an alkoxy or alkylthio group; or R^9 together with R^{10} represent an alkylenedioxy or alkylenedithio group; and R^3 and R^4 each represent a hydrogen atom or an alkyl or alkanoyl group,

and acid addition salts thereof.

2. Benzylpyrimidine derivatives according to claim 1, wherein R^1, R^2 and n have the significance given in that claim, R^6 represents an oxygen atom and R^7 represents a hydrogen atom or an alkyl or alkoxy group; or R^6 represents a hydroxyimino group and R^7 represents an alkyl group; or R^6 and R^7 together with the carbon atom to which they are attached represent a nitrilo group; R^3 and R^4 each represent a hydrogen atom or an alkyl group; R^8 and R^9 each represent a hydrogen atom or an alkyl group and R^{10} represents a hydroxy, alkoxy or $-N(R^3)(R^4)$ group; or R^9 and R^{10} each represent an alkoxy or alkylthio group; or R^9 together with R^{10} represent an alkylenedioxy or alkylenedithio group; or A^1 represents a trifluoromethyl group.

3. Benzylpyrimidine derivatives according to claim 1, wherein R^1 and R^2 each represent an alkyl group and A^1 represents a hydroxymethyl group which is C-monoalkylated or dialkylated or an alkoxymethyl group which may be C-monoalkylated or dialkylated or an alkylcarbonyl group.

4. α - (2,4 - Diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester.

5. α - (2,4 - Diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid isopropyl ester.

6. α - (2,4 - Diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid butyl ester.

7. α - (2,4 - Diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid ethyl ester.

8. 4 - [(2,4 - Diamino - 5 - pyrimidinyl) - methyl] - 2,6 - dimethoxy - benzyl alcohol.

9. α - (2',4' - Diamino - 5' - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester 3' - oxide.

10. α - (2',4' - Diamino - 5' - pyrimidinyl) - 2,6 - dimethoxy - p - toluic acid methyl ester 1' - oxide.

11. α - (2,4 - Diamino - 5 - pyrimidinyl) - 2,6 - diethoxy - p - toluic acid ethyl ester.

12. 4 - [(2,4 - Diamino - 5 - pyrimidinyl) - methyl] - 2,6 - diethoxy - α,α - dimethyl - benzyl alcohol.

13. α - (2,4 - Diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - p - toluonitrile.

14. 2,4 - Diamino - 5 - (4 - aminomethyl - 3,5 - dimethoxy - benzyl) - pyrimidine.

15. N - [4 - (2,4 - Diamino - 5 - pyrimidinyl) - 2,6 - dimethoxy - benzyl] - acetamide.

16. 4' - [(2,4 - Diamino - 5 - pyrimidinyl) - methyl] - 2',6' - diethoxy - acetophenone.

17. 4' - [2,4 - Diamino - 5 - pyrimidinyl) - methyl] - 2',6' - dimethoxy - acetophenone.

18. 4 - [(2,4 - Diamino - 5 - pyrimidinyl) - methyl] - 2,6 - dimethoxy - α - methyl - benzyl alcohol.

19. 4 - [(2,4 - Diamino - 5 - pyrimidinyl) - methyl] - α - ethyl - 2,6 - dimethoxy - benzyl alcohol.

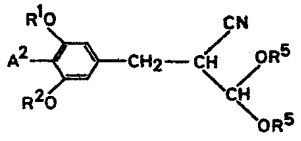
20. 2,4 - Diamino - 5 - [3,5 - dimethoxy - 4 - (methoxy - methyl) - benzyl] - pyrimidine.

21. 4 - [(2,4 - Diamino - 5 - pyrimidinyl) - methyl] - 2,6 - dimethoxy - α,α - dimethyl - benzyl alcohol.

22. 4 - [(2,4 - Diamino - 5 - pyrimidinyl) - methyl] - α,α - diethyl - 2,6 - dimethoxy - benzyl alcohol.

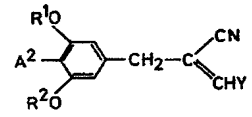
23. A process for the manufacture of the benzylpyrimidine derivatives claimed in claim 1, which process comprises

a) reacting a compound of the general formula



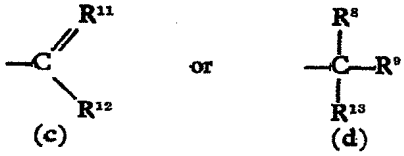
(IIa)

or



(IIb)

wherein R^5 represents an alkyl group, Y represents a leaving group and A^2 represents a trifluoromethyl group or a group of the formula



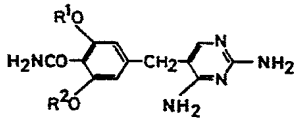
(c) (d)

in which R^{11} represents an oxygen atom and R^{12} represents an alkoxy group; or R^{11} together with R^{12} and the carbon atom to which they are attached represent a nitrilo group; R^{13} represents a hydroxy, alkoxy or $-N(R^3)(R^4)$ group; and R^1, R^2, R^3, R^4, R^8 and R^9 have the significance given in claim 1,

with guanidine,

or

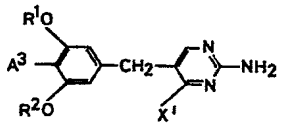
b) dehydrating a compound of the general formula



(III)

wherein R^1 and R^2 have the significance given in claim 1,
to the corresponding nitrile,
or

c) reacting a compound of the general formula



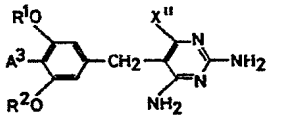
(IV)

wherein X′ represents a chlorine or bromine atom or an alkylthio or alkylsulphonyl group and A^3 represents a trifluoromethyl group or a group of the formula

(c) (e)

in which A^{11} represents an oxygen atom and R^{12} represents an alkoxy group; or R^{11} together with R^{12} and the carbon atom to which they are attached represent a nitrilo group; and R^{14} represents an alkoxy or $-N(R^3)(R^4)$ group; or R^9 together with R^{14} represent an alkylenedioxy group, and R^1, R^2, R^3, R^4, R^8 and R^9 have the significance given in claim 1,
with ammonia,
or

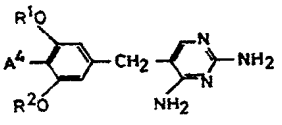
d) replacing the substituent denoted by X″ in a compound of the general formula



(V)

wherein R^1 and R^2 have the significance given in claim 1, A^3 has the significance given earlier in this claim and X″ represents a chlorine or bromine atom or a hydroxy group,
by a hydrogen atom,
or

e) reductively cleaving the group A^4 in a compound of the general formula

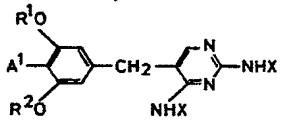


(VI)

wherein A^4 represents the group $-CO-CH(R^8)-SO_2-CH_3$, $-CO-CH(R^8)-SO_2-$ phenyl or $-CO-CH(R^8)-SO-CH_3$ and R^1, R^2 and R^8 have the significance given in claim 1,
to the acetyl group,
or

f) subjecting a compound of formula I given in claim 1 in which n stands for zero to N-oxidation,
or

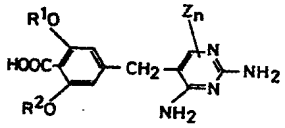
g) cleaving off the amino-protecting group or groups in a compound of the general formula



(VII)

wherein X represents a hydrogen atom or an amino-protecting group (at least one X representing an amino-protecting group), and R^1, R^2 and A^1 have the significance given in claim 1,
by hydrolysis or hydrogenolysis,
or

h) subjecting the carboxyl group in a compound of the general formula



(Ia)

wherein R^1, R^2, Z and n have the significance given in claim 1,
to esterification or to reduction to the aldehyde group,
or

i) subjecting the carbonyl group in a compound of formula I in which A^1 represents an alkylcarbonyl group and R^1, R^2, Z and n have the significance given in claim 1 to condensation with hydroxylamine to give the hydroxyimino group, or to reductive amination, or to reduction to give the alcohol, or to ketalisation or thioketalisation, or to reaction with a Grignard compound to give a homologous alcohol,
or

j. subjecting the alkoxycarbonyl group in a compound of formula I in which A^1 represents an alkoxycarbonyl group and R^1, R^2, Z and n have the significance given in claim 1 to reaction with a Grignard compound to give the ketone or the secondary or tertiary alcohol; or to reduction to give the alcohol,
or

k) alkylating an alcohol function contained in A^1 in a compound of formula I or oxidis-

ing said function to give the carbonyl group, or

l) reducing a nitrile group denoted by A^1 in a compound of formula I hereinbefore to give the aminomethyl group or to give the aldehyde group,
or

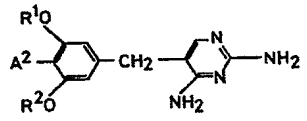
m) cleaving off a ketal or thioketal group contained in A^1 in a compound of formula I,
or

n) hydrolysing off the acyl group present in a compound of formula I in which A^1 represents a group of the formula

$$—CH_2—N(R^5)—COR^5$$

wherein R^5 has the significance given earlier in this claim and R^5 has the significance given in claim 1, and, if desired, converting a base obtained into an acid addition salt.

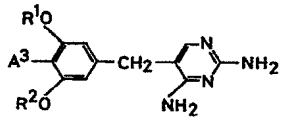
24. A process according to claim 23, wherein a compound of the general formula



(Ib)

wherein R^1 and R^2 have the significance given in claim 1 and A^2 has the significance given in claim 4,
is manufactured according to embodiment (a).

25. A process according to claim 23, wherein a compound of the general formula



(Id)

wherein R^1 and R^2 have the significance given in claim 1 and A^3 has the significance given in claim 4,
is manufactured according to embodiment (c) from a compound of formula IV in which X′ represents a chlorine or bromine atom or according to embodiment (d) from a compound of formula V in which X″ represents a chlorine or bromine atom.

26. A process according to claim 23, wherein there is manufactured in accordance with embodiment (f) a compound of formula I in which A^1, R^1 and R^2 have the significance given in claim 1 with the proviso that, in the group A^1, R^3 and R^4 do not represent an alkanoyl group.

27. A process according to claim 23, wherein a compound of formula I in which A^1, R^1 and R^2 have the significance given in claim 1 and n stands for zero is manufactured in accordance with embodiment (g) from a compound of formula VII in which the two symbols X represents amino-protecting groups.

28. A process according to claim 23, wherein a compound of formula I in which R^1, R^2, Z and n have the significance given in claim 1 and A^1 represents an alkoxycarbonyl or aldehyde group is manufactured in accordance with embodiment (h).

29. A process according to claim 23, wherein the carbonyl group present in a compound of formula I in which A^1 represents an alkylcarbonyl group and R^1, R^2, Z and n have the significance given in claim 1 is condensed with hydroxylamine to give the hydroxyimino group, or reductively aminated, or reduced to the alcohol, or ketalised or thioketalised, or reacted with a Grignard compound to give a homologous alcohol.

30. A process according to claim 23, wherein the alkoxycarbonyl group present in a compound of formula I in which R^1, R^2, Z and n have the significance given in claim 1 and A^1 represents an alkoxycarbonyl group is reacted with a Grignard compound to give the ketone or reduced to the alcohol.

31. A process according to claim 23, wherein an alcohol function contained in A^1 in a compound of formula I is alkylated or thioalkylated or oxidised to the carbonyl group.

32. A process according to claim 23, wherein a nitrile group denoted by A^1 in a compound of formula I is reduced to the amino group or to the aldehyde group.

33. A process according to claim 23, wherein a ketal or thioketal group present in A^1 in a compound of formula I is cleaved off.

34. A process according to any one of claims 23 to 33 inclusive, wherein there is manufactured a compound of formula I in which R^1 and R^2 each represent an alkyl group and A^1 represents a hydroxymethyl group which is C-monoalkylated or dialkylated or an alkoxymethyl group which may be C-monoalkylated or dialkylated or an alkylcarbonyl group.

35. A process as claimed in claim 23 for the manufacture of the benzylpyrimidine derivatives claimed in claim 1, substantially as hereinbefore described with reference to the Examples.

36. A benzylpyrimidine derivative as claimed in claim 1, when manufactured by the process claimed in any one of claims 23 to 35 inclusive.

37. An antibacterial composition which contains a benzylpyrimidine derivative as set forth in claim 1 in association with a compatible carrier material.

38. An antibacterial composition according to claim 37, wherein an antibacterially active sulphonamide is also present.

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